

ISSN 1751-0716

IBSscientific

An Open Access Peer Reviewed Magazine

Volume 2 Issue 2 | April 2006 | <http://www.ibscientific.net>



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IBS_{cientific} ... A Dream Becoming a Reality!

WE are quite accustomed to link ambitions to dreams that are hard to realise and also elevate difficulties to the rank of impossibility. IBScientific with its achievements has proved its ability to break these misconceptions and redefined difficulty as “challenge” which was taken with excitement in order to transform what was an unstructured ambition in the beginning into a well developed reality.

Lots of considerable efforts have been put forward in order to realise the dream of many groups as well as individuals. The dream was to open an Algerian Scientific window, which has been locked for long. IBScientific has broken the locks and opened the window, the view is science and technology and the frame is a group of young researchers whose goal is to ensure the view is always unique.

In this issue IBScientific is celebrating its first anniversary. The magazine has become widely known, has outstandingly improved and its popularity has remarkably increased. Quality and diversity in topics have attracted many academics and senior researchers and is still aiming for more. IBScientific magazine is now registered as an international publication after it has recently obtained its own ISSN, and has hence become a recognised quarterly publication across any library in the world. Furthermore, as promised in the

inaugural issue, this month's issue witnesses the birth of IBS Journal of Science, which is also a registered as a separate publication.

Found in this issue are some exciting articles, hot news, the new journal and many more. Also, find out about IBScientific first annual meeting, a one day conference, which discusses science and technology present state and ways of improvements.

Before I sign my name down I want to thank everyone who has had a hand in this noble project, especially the IBScientific board who are truly working hard in order to achieve high standards and perfection and ensure their readers are satisfied. To our faithful readers, our gratitude and appreciations; you want it to happen and so do we and here you are, it is all about decision. So keep your faith in IBScientific and we will ensure you quality, originality and diversity.

I hope you will enjoy flipping through this issue. Your remarks, suggestions and criticisms are most welcome. “Unless a picture is missing some parts, it won't be completed”

Elhadj BENKHELIFA

IBScientific Advertisement & Marketing Officer

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Subscription to IBScientific is free. For more details, email editorial@ibscientific.net.

IBScientific is a registered Journal: ISSN 1751-0716.

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Reproductive Science

Fils à Maman



YOU owe a big chunk of your energy generators to your very dear mother. Scientists have established a long time ago that during fertilisation most mitochondria from sperm gets diluted, with the female's egg containing one thousand fold more of the organelle. Recently, the process has been filmed by a research team who reported that once the egg is fertilized the sperm mitochondrial DNA is destroyed. The study however, which was published online the week of 23 January in the Proceedings of the National Academy of Sciences, still gives no answer to whether the sperm or the egg is behind the desintegration. Nevertheless, the outcome lays to rest the idea that the mitochondria's maternal lineage is due to chance.

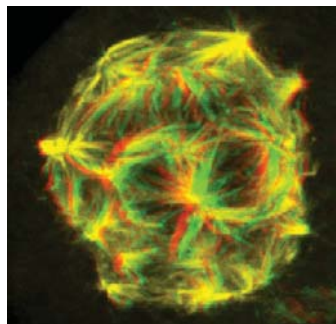
Y.M. Source: PNAS (Proceedings of the National Academy of Sciences)

Human Health

HIV Circumcised

MALE circumcision can protect both women and men from HIV infection, a study of Ugandan medical records has shown. Circumcision has been known for years to reduce the likelihood of men catching HIV from infected partners. The apparent reason being inner cells of the male foreskin, the skin removed by circumcision, can hold nine times more virus than

the outer cells of the male sexual organ, and is the main entry point for HIV. Cutting off the foreskin, as many doctors suggest is cutting off the virus's gateway to the body. Recently, researchers at the Johns Hopkins Medical Institutions in Baltimore, Maryland, suggest it might as well benefit women. Women with circumcised partners are 30% less prone to infection, they say, because they are less exposed to the virus.



The team lead by Ronald Gray have studied the medical records of more than 300 Ugandan couples from 1994 to 2001. Initially, all men involved in the study were HIV positive, whereas all the women were HIV negative. Of the men, 44 were circumcised and 299 were not. The medical records show that in average, females with circumcised partners caught HIV at an annual rate of 6.6% compared to 10.3% in females whose men were uncircumcised.

The study has been presented on 8 February at the 2006 Conference on Retroviruses and Opportunistic Infections in Denver, Colorado.

However it remains true that benefits of circumcision can only be proved with proper full medical trials, not ignoring other factors such as constraints on relationships, sexual practices and hygiene.

Y.M. Source: Nature Drug Discovery

Cancer Biology

Diet, Diet, Diet !!!

THE question regarding the role of diet as a cancer-risk modifier remains puzzling. A study led by Sheila Bingham published in Cancer Research [1] has shown that eating large quantities of red meat can increase the risk of bowel cancer though the formation of DNA damaging substances in the gut. The study showed increased levels of DNA damage in cells from the lining of the colon from people with a diet high in red meat compared to vegetarians. Such damage can increase the risk of developing cancer, say researchers at the Medical Research Council's (MRC) Dunn human nutrition unit in Cambridge.

These findings follow a major European study conducted last year which revealed that people who eat two portions of red or processed meat a day increase their risk of bowel cancer by 35% compared with those who eat one portion weekly. The research monitored the diets of nearly half a million men and women in 10 countries over five years. The new study looked for changes that could underlie the association between diet high in red meat and the increased risk of bowel cancer.

The scientists assessed the alterations in DNA from 21 volunteers, who were put onto three different diets for 15 days. The first diet was high in meat; the second was vegetarian, and the third contained meat but also contained higher levels of fibre. The researchers found "consistent and significant" increase in DNA damage during the consumption of the red-meat diet when compared with the vegetarian, while damage was intermediate with the red meat/high fibre diet.

The DNA damage was specific to substances called N-nitrosocompounds (NOC) found in increased levels in the large bowel of red meat eaters. Some of these compounds

are thought to combine with DNA and destabilise it, making it more likely to undergo harmful changes that increase the risk of cancer. Fibre may reduce the risk by getting rid of damaged cells.

Colin Blakemore, the MRC's chief executive, said: "Large bowel cancer is the second most common cancer in western countries and nearly 1m cases occur each year worldwide. This latest study, together with the compelling epidemiological evidence published last year, is an important step towards understanding and potentially preventing this common disease." However, the Meat and Livestock Commission pointed out that the research assessed people eating 420g of red meat a day, over five times more than the average man's quota of 80g, and over eight times the average woman's intake of 50g. An average fillet steak weighs 140g and an average burger about 100g.

A.K. Source: Cancer Research.

Anatomy

Okay Then, Anatomy is Still Changing in 2006....!!!

IF you knew that mice have been extensively used in biological and medical research for over a century, you would think that specialized-scientists would know the mouse

[1] Lewin M.H., et al. Cancer Research, 66, 1859-1865. 2006.

[2] Terzowski G., et al. Science. www.scienceexpress.org. 10.1126/science.1123497 (2006).

[3] BBC News Science & Technology, March 20, 2006. <http://news.bbc.co.uk/go/pr/ft/-/1/hi/sci/tech/4825388.stm>.

[4] Press release, March 16, 2006. Delft University of Technology, Holland. <http://www.tudelft.nl/live/pagina.jsp?id=64b37753-31f3-4636-bf72-0d9f710ea7ce&lang=en>.

[5] <http://tribler.org/>

body organs inside out. But hang on a minute... actually it is not as simple as it sounds, because German researchers say they have discovered a whole new organ in mice.

The thymus, a pink-grey lump of tissue located in the chest above the heart and with roughly the size of a pea. The thymus helps in the production of T-cells, the infection-fighting cells of the immune system. Up till recently the mouse was believed to have one thymus.

Now a research team led by Hans-Reimer Rodewald at the University of Ulm in Germany has discovered a smaller, second thymus hidden in the necks of lab mice [2]. This is a very significant finding, and this discovery raises questions about some immunology studies in mice. Typically, immunologists interested in the function of the immune system and the development of T cells slice-out the main thymus of mice in order to study how the system works and how T cells are produced in other organs such as the gut and skin. Having a second thymus means that in these studies many of the mice still had a functional thymus in their necks, which could have confounded the results.

It is interesting because biologists already knew that other mammals, including some humans, possess an extra thymus in their necks. In fact, studies from as early as the 1940s suggest that five out of six human fetuses have a second thymus in the neck. The idea that the mouse has a second thymus was suggested in the 1960s. However, this is the first study to describe the actual presence of a second working thymus standard in mice.

Rodewald's team found the new organ when studying animals with defects in the chest thymus; they came across tissue that looked like that from the thymus but it was in the neck just by the windpipe. The team found that almost all healthy mice of certain strains have this second neck thymus with a size of a large pinhead. The research

team then went on to investigate the identity of the new organ and they found it behaved like the old thymus.

Scientists are intrigued by the origin of the second thymus. The big interest in this organ reflects its importance in development of the immune system. Scientists also hope to identify stem cells from which the thymus sprouts, and perhaps use them to regenerate the organ in bone-marrow transplant patients whose thymus is damaged by treatments.

A.K. Source: Science Magazine.

Computing

Organic Electronics

A research team composed of professionals and academics from Merck Chemicals, Southampton, UK; Palo Alto Research Center, California; Department of Materials Science and Engineering, Stanford University; and the Stanford Synchrotron Radiation Laboratory is leading research on a new material that could rival silicon in electronic devices.

The new material, reported in Nature Materials is simply an organic polymer [3]. Its use in the electronics industry could cut the cost of production as it can be laid out using simple printing techniques. In addition to this, the team adds that its invention could bring electronic paper into common use.

The team used chemical modifications to increase the speed at which polymers conduct electricity. The new semi-conducting polythiophene has been tweaked to change its molecular structure. Its new structure enables it to carry electrical signals as well as dissolve to become ink. It can then be printed using traditional inkjet printers. These modifications give the material important advantages over silicon, which is slow and expensive to produce and generates a large amount of waste.

However, the new material is unlikely to be able to rival silicon in the manufacture of high-speed computer chips. It will most likely be used in areas where silicon struggles to compete.

S.N. Source: BBC NEWS Science & Technology

P2P Television

A new peer-to-peer system for sharing television programs has been launched during The Workshop on Technical and Legal Aspects of Peer-to-Peer Television held in Amsterdam on the 17th of March 2006 [4] The system, called Tribler [5] is based on open-source software and has been a centre of interest for many broadcasting corporations, TV stations and cable and telecommunications companies.

While the current method makes use of centrally located computer systems, research is now being conducted (among other institutes) into TV distribution through peer-to-peer systems. The use of this type of transmission for TV distribution will enable large groups of ordinary PCs to share TV programs. The method which has been the focus of research at Delft University of Technology, Holland, will also open new ways to TV stations operating through the Internet.

S.N. Source: Delft University of Technology, Holland.

Immunology

Immunologists: Let's vaccinate the heart!

Cardiologists: What?

A vaccine for atherosclerosis: A novel therapy in the management of coronary artery disease.

Atherosclerosis is an important factor in the development of coronary artery diseases. It is widely accepted that inflammation plays a role in the formation of an atherosclerotic lesion and its destabilisation. As a result of this, a novel approach in treating atherosclerosis is being evaluated: immunomodulation.

There are three main immune cells involved in atherogenic plaque formation: macrophages, CD4+T-cells and dendritic cells. These cells function as hunters of foreign bodies (e.g. Bacteria) and either present them as small pieces, usually proteins called antigens, or attack them directly. These cells react to autoantigens (antigens made by the body's own cells) such as oxidised low density lipoprotein (oxLDL), B-2 glycoprotein I and heat Shock Proteins (HSPs), which subsequently trigger autoimmune and inflammatory responses, which result in acute coronary syndrome. Based on this principle, immunisation has attracted many researchers and the results from current experiments are encouraging.

Both atherogenic and atheroprotective immune effects are involved in the pathogenesis of atherosclerosis. IL-12 for an example is a key inducer of type-1 T helper cell, which triggers an inflammatory response in human atherosclerotic lesions. In an experiment, on a mouse model, conducted by Hauer et al., blockade of endogenous IL-12 resulted in a significant reduction in atherogenesis. Furthermore, vaccination against IL-12 improved plaque stability.

In contrast to IL-12, both IL-5 and IL-10 are atheroprotective. IL-5 mediates the modulation of protective natural immunity to oxLDL and its deficiency was found to accelerate atherosclerosis. IL-10, on the other hand, is a potent monocyte deactivator. It was found that recombinant human IL-10 reduced post injury intimal hyperplasia, which subsequently reduced stent intimal growth and therefore prevent in-stent restenosis.

In addition to interleukins, other molecules such as HSPs have attracted many researchers. Some studies reported an association between the concentration and type of HSP and the severity of and progression of cardiovascular diseases. Other studies, reported that immunisation of rabbits with HSP65 resulted in arteriosclerosis. On the other hand immunisation against HSP70 resulted in acceleration of intimal thickening in injured carotid arteries of rats.

It was mentioned earlier that oxLDL is an autoantigen in atherosclerosis. Studies revealed that immunisation of animals with in vitro

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oxLDL resulted in a protective effect and decreased atherosclerosis as a result of the over-expression of IgM and IgG antibodies against oxLDL. This suggests a possibility of an immunomodulatory therapy targeting oxLDL. Researchers at the University of California, Los Angeles have identified about 100 antigenic epitopes in human apo B-100. Two epitopes have been so far evaluated by Shah and his colleagues [6, 7]. Only one peptide (peptide-2) immunisation was shown to reduce aortic atherosclerosis by 40% and plaque inflammation by 80% compared to controls. In addition to this, peptide-2 immunisation of mice at 16 weeks of age reduced the progression of aortic lesions. In addition to this, Nilsson, Hansson and Shah [8] reported that results from other studies suggest that immunisation can reduce atherosclerosis by 50% to 60%. This implies that the vaccine does not give absolute immunity compared to those targeting infectious diseases.

It is important to bear in mind that if the therapy is proven to be effective in the treatment and prevention of atherosclerosis, other aspects such as risks and potential side effects should be considered before bringing it to clinical practice. So, in years to come, another vaccine may be introduced in the routine childhood immunisation programme!

S.B. Source: Cardiosource: American College of Cardiology.

History



1001 Inventions Highlight Muslim Contributions to the World!

A cup of coffee, windmills, carpets, soap and the fountain pen, what

do they all have in common? Apparently they were all invented by Muslims.

The newly opened exhibit entitled 1001 Inventions in Manchester, UK, does just this in a fascinating exploration of innovations and inventions that have contributed to world history. It uncovers the Islamic civilisation's overlooked contribution to science, technology and art during the dark ages in European history. The exhibit is currently being showcased at The Museum of Science & Industry in Manchester from March 8 to June 4, 2006. From there it will move around the UK to different museums. The exhibition is supported by a host of government and private sector initiatives such as the Home Office and the Department for Trade and Industry and includes over 40 interactive exhibits of various kinds. It is separated into seven different zones for discovery including: home, school, market, hospital, town, world, and universe. An interactive web log also allows visitors to the exhibit's website to record their comments and create discussions on various topics ranging from the world's first soft drink to music and gardening.

It lifts the veil on hundreds of innovations - from kiosks and chess through to windmills and cryptography - that are often popularly associated with the western world but originate from Muslim scholarship and science.

Based on more than 3,000 peer-reviewed academic studies, the exhibition charts Islamic innovations during ten decades of "missing history" spanning from the 6th to the 16th century and covering an area stretching from China to southern Spain.

One example of the inventions featured is that of Ibn Hazm, an Andalusian astronomer who proved that the world was round 500 years before Galileo made his discovery.

Professor Salim Al-Hassani, chairman of the Foundation for Science, Technology and Civilisation (FSTC), which organised the exhibition, said: "The extent to which Muslims have contributed to Western civilisation is not generally well known. Yet these ancient scholars from the Islamic world gave us many of the everyday things we use such as coffee, soap and clocks...

this exhibition shows that Muslims have always shared the heritage that provides a platform for developments that makes the Western world tick".

The organisers also hope to use the compilation to bring about an audit of the national curriculum to ensure it recognises Islamic achievements and the full extent of knowledge transfer between civilisations through the ages. Professor al-Hassani said: "If you ask the average person where their spectacles or camera or fountain pen come from, few people would say Muslims... a lot of these scientific and cultural developments are accepted as fact in the academy, but the vast majority of people - because of the nature of the education system - are completely unaware of their origins". "For a lot of children in schools, the history of science seems untouchable and remote", said Yasmin Khan, the exhibitions project manager. "We need to change the way we explain civilisation's progress in our schools".

Professor Mark Halstead, a lecturer in moral education at Plymouth University, said there was scope in the existing curriculum to teach the contributions of Islamic civilisation, but teachers required better training. "Islam needs to take its place alongside other historic groups, such as the ancient Romans and Greeks", he said.

"When Europe was living in the dark ages, Islamic civilisation was blossoming, and the advances during this period are more relevant to the modern world than those of the Ancient Egyptians and Aztecs".

For further information, some fascinating facts and events programme visit: www.1001inventions.com

S.A. Sources: <http://www.dinar-standard.com>, www.aljazeera.net, www.guardian.co.uk and www.1001inventions.com.

Regenerative medicine

More Stem Cells for Men

A group of researchers led by Gerd Hasenfuss from the Georg August University, (Göttingen, Ger-

many) announced the discovery of reprogrammable cells in the testes of adult mice, which behaved like stem cells. A discovery that has drawn immediate attention from the scientific media as well as the pharmaceutical industry, for its therapeutic promises.

As Hasenfuss's team reported in Nature [9], the stem cells discovered come from sperm-producing stem cells in mice. It is not clear whether these cells found in the testes have the ability to make all other types of bodily cells, as embryonic stem cells can. However, the research team managed to multiply these cells by 700 fold, after which cells formed embryo like structures in 4 out of 15 cases. When injected into early embryos, these cells contributed to the formation of various organs of the resulting mouse. Supported by in vitro experiments, the derived cells differentiated into several different types of cell, including brain, heart and skin cells.

Now the team is hoping to move the studies to humans, the team reports receiving tissue samples from testicular-cancer patients, and hoping to extract stem cells from them. Hasenfuss thinks that, eventually, a simple biopsy could extract the necessary cells. Such cells would be match with the patient, which makes them less likely to be rejected if used in therapy. Between hopes and fears: stem cell research still waits for the breakthrough.

A.K. Source: Nature.

[6] Shah PK, Chyu KY, Fredrikson GN, Nilsson J. Immunomodulation of atherosclerosis with a vaccine. *Nat Clin Pract Cardiovasc Med* 2005; 2:639-46

[7] Chyn KY, Zhao X, Reyes OS et al. Immunisation using apo B100 related epitope reduces atherosclerosis and plaque formation in hypercholesterolemic aop (-/-) mice. *Biochem Biophys Res Commun* 2005; 338:1982-9

[8] Nilsson J, Hansson GK, Shah PK. Immunomodulation of atherosclerosis implication for vaccine development. *Arterioscler Thromb Vasc Biol* 2005;25:18-28

[9] Nature 24 March, doi:10.1038/nature04697

What to Optimise?

Preview by:
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Just like most of my generation, BASIC was the first programming language I learnt as a fresher in the world of programming. One soon realises that such a language can never produce really fast programs because it is an interpreted language, meaning that the computer reads every instruction, interprets it and then executes the required action. The other option at the time was to use ‘Machine Language’, but that was too hard for an average programmer to try out, let alone for beginners!

A few years later, I discovered C; it had what BASIC missed: Instructions no longer had to be slowly interpreted by the computer, these were instead “compiled” beforehand into ‘Machine Language’, which the computer can execute right away, close to full speed.

The article by Mr. Naci [1] nicely describes the concept of Programming Languages, then introduces the important notion of Compilers and briefly sketches their history. Compilers involve a lot of theory and craft in trying to produce an efficient code equivalent to what was written by the programmer. To this end, a few decisions have to be made in order to optimise the performance of the resulting program.

The main hurdle that compiler designers had to overcome was to increase the speed of execution of simple and nested loops. A lot of progress has been done on this side and numerous techniques called “Loop Transformations” are known. These, however, have various and sometimes serious limitations due to the inherent nature of the program itself.

Alternatives to loops transformations had to be studied. Amongst the most effective methods are “Data Transformations”. These excel in many areas where Loop Transformations fail, and compete with them in others.

After a very good discussion of the two techniques, which constitute the main research topics in the field of Compiler Optimisation, Mr. Naci concludes that a more unified framework might be possible to achieve optimal results.

Treat yourself to some very good primer reading!

[1] Naci, S. (2006). **Primer: Compiler Optimisation. Improving Locality via Loop and Data Transformation.** *IBScientific*, 2 (2), 50-55.

Drug Safety: Catching the Pill

Preview by:
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Clinical trials in drug discovery are a key step for the investigation of the safety and efficacy of newly discovered drug molecules. The year 2004 has been a year that the drug discovery community would rather forget. Ever since, questions about pricing schemes, clinical trials registries and the role of government-funded research in drug discovery have been raised in public forums, and culminated in perhaps the biggest debacle to rock the industry in recent years —the withdrawal of rofecoxib (Vioxx; Merck) after a study in patients with colon cancer indicated that it doubled the risk of heart attacks and stroke in those who took it for longer than 18 months. It seems that current safety systems sometimes fail to notice that approved drugs are causing serious adverse effects.

Understanding some of the basic principles and procedures involved in testing drugs would give Governments and authorisation bodies a better insight for drug-safety policies. In the current issue, not only does Y. Mehellou [2] gives a must-read account of the story of a drug as it proceeds from point of entry through its journey into the body, but also an enlightening overview of pharmacokinetics parameters which are very much at the heart of safety

trials in drug discovery.

[2] Mehellou, Y. (2006). *Pharmacokinetics in clinical trials of drug development*. IBScientific, 2 (2), 47-49.

The Universe: An Insider's Tale

Preview by:
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It is hard to think of a more fascinating subject for scientific enquiry than the investigation of our universe's early origins. How did the universe begin? Did it ever have a beginning? Is the universe

eternal or will it end one day? Until about 100 years ago, such questions belonged to the realm of philosophy and metaphysics.

In the early part of the 20th century, astronomical observations led scientists to believe that the universe was expanding. Extrapolating back in the past, the logical conclusion was that the universe emerged from a gigantic implosion of a singularity about 15 billion years ago. In 1964, scientists were able to detect the cosmic background radiation, the "glow" left over from the explosion itself: suddenly humans found themselves in a position where they could literally see the Big Bang, measure its parameters, compare data to theory and map out a credible theory for the evolution of the universe from a time of approximately 10^{-20} s after the instant of creation to the present time.

Before the first billionth of a trillionth of a second...

All fine so far, but what has the Big Bang got to tell us about the creation of space, time, matter, light, and energy? In short, nothing. In this context can it really claim the theory of creation of the universe title?

Leon Lederman, a Nobel Prize winner, said about the Big Bang

"In the very beginning, there was a void, a curious form of vacuum, a nothingness containing no space, no time, no matter, no light, no sound. Yet the laws of nature were in place and this curious vacuum held potential. A story logically begins at the beginning, but this story is about the universe and unfortunately there are no data for the very beginnings--none, zero. We don't know anything about the universe until it reaches the mature age of a billionth of a trillionth of a second. That is, some very short time after creation in the big bang. When you read or hear anything about the birth of the universe, someone is making it up--we are in the realm of philosophy. Only God knows what happened at the very beginning."

Stephen Hawking, a modern cosmologist also said, "the actual point of creation lies outside the scope of presently known laws of physics,"

By all means, do read Samir Rihani's excellent review [3] that highlights most of the aspects you can find about this intriguing and fascinating theory for the creation of the universe. But just remember, the scientific adventure has just started; nature has not revealed all its secrets yet, we might still be surprised.

[3] Rihani, S. (2006). *Big Bang Theory*. IBScientific, 2 (2), 42-45.

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IBScientific

BIG BANG THEORY

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Mankind has always questioned his existence in the middle of the universe, and throughout our brief history in this planet, a lot of time and effort has been spent to try and answer fundamental questions like: How did the universe begin? How did matter come to exist? Thanks to modern science, we are now in a position to understand the creation of the universe. In this article we will state observational and theoretical pieces of evidence that support the Big Bang theory. Although this theory is not complete, it provides a powerful framework to understand the evolution of the universe. However if we would like to know about the moment of creation, the Big Bang theory will need to use a theory of Quantum Gravity in order to give an appropriate description of that moment.

Cosmology is the scientific study of the large scale structure and properties of the universe as a whole. It endeavours to use scientific methods to understand the origin, evolution and ultimate fate of the entire universe. The science of cosmology is mainly based on observations that we make on our universe and also includes the formation of theories or hypotheses about the universe which make

specific predictions for phenomena that can be tested with observations. If the observations reveal the same outcome as predicted by the theory then they count as a proof for that specific theory. However, if the observations were not compatible with the theory, the latter has to be abandoned or revised, in order to account for the observed phenomena.

The ultimate purpose of a theory in the field of cosmology is to try and model the universe using a certain set of rules to explain the different phenomena observed.

This leads to the construction of what we call Cosmological Models; which are descriptions of our universe as a whole.

Newtonian Cosmology failed to describe our universe and the cosmological model derived from the Newtonian definition of

gravity, was unstable. This is because the model assumes the universe to be static and infinite.

This model also leaves us with a major puzzle as to why the night sky is dark. If space goes on for ever containing an infinite number of stars, then at any point in the sky we should be able to see a star, and the entire sky should blaze like the surface of the Sun even at night. This is known as Olbers's paradox (Kaufman & Freedman, 1999, page 698).

In 1915 Albert Einstein changed our view of space, time and the universe when he formulated the general theory of relativity. After this achievement Einstein applied the theory to the whole universe and he found that his equations could not produce a static universe.

According to the General theory of relativity the universe must be either expanding or contracting. Influenced by the idea of a static universe Einstein introduced the so-called cosmological constant ("antigravity" force), which is a force built into the very fabric of space and time (Hawking, 1988 page 40) and acts as to balance the gravitational attraction, so the universe would be static and not collapse. However the Russian physicist and mathematician Alexander Friedmann adopted the idea of an expanding universe which was consistent with the general theory of relativity and Hubble's observations. It was these observations that caused Einstein to be quoted in his last years as calling the cosmological constant¹ "the greatest blunder of my life" (Kaufman & Freedman, 1999, page 699).

In 1920 Hubble made one of the greatest discoveries in cosmology; he found that the light coming from remote galaxies was red shifted and according to the Doppler Effect this meant that galaxies are moving away from us. Hubble also found a simple formula relating the speed of the galaxy v with its distance from the earth d :

$$v = H_0 d \quad (1)$$

¹ The cosmological constant is still being used in today's models to account for the acceleration of the expansion. The origin of this acceleration is not known and is usually termed "dark energy".

Received: November 20, 2005; Revised: March 16, 2006; Accepted: March 25, 2005; Published April 16, 2006.

The author declares no conflict of interest.

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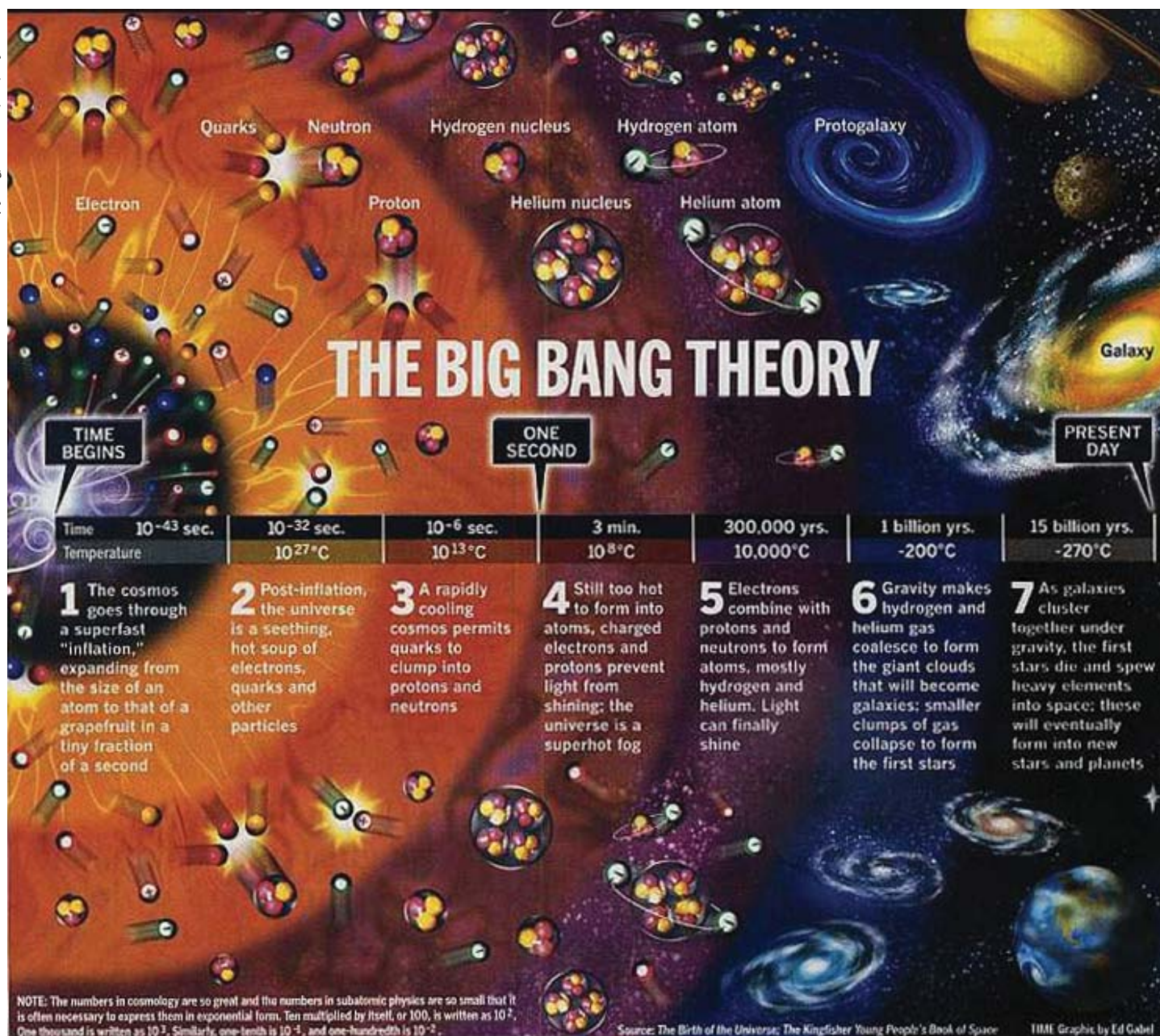


Figure 1: The time line of the development of the universe according to the Big Bang theory

where H_0 is the Hubble constant. Because galaxies are moving away from us we say that the universe is expanding. The Hubble law also indicates that the universe has been expanding for billions of years.

After discovering the expansion of the universe two cosmological models were formed in order to account for this new discovery. The first one was the Steady State Theory which assumes that as galaxies moved away from each other, new ones were formed so as to keep the density of the universe the same everywhere. However this theory had to be abandoned as it contradicted many observations made at the time.

The second model (which is the one of interest for us) is the Big Bang model. This is a very simple model; it suggests that as we go into the past the matter in the universe must have been closer and closer to each other, until around 15 billion years ago where the entire universe was contained in a single point called the Big Bang singularity. This singularity provided the initial explosion (the Big Bang) which started the expansion of the universe.

Evidence for the Big Bang Theory

The Big Bang theory is today's most dominant scientific theory about the origin of the universe. According to the theory the universe started some 15 billion years ago when it was compressed into a single point, in which the density of the universe and curvature of space-time would have been infinite. (We don't know if something existed before the Big Bang, what caused the Big Bang and where the singularity came from). or even (did time exist?), a tremendous explosion happened, not only creating

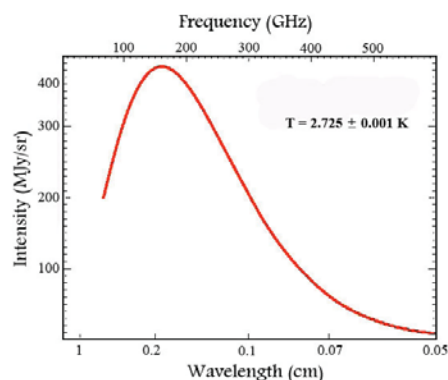


Figure 2: Spectrum of the Cosmic Microwave Background

fundamental subatomic particles but even space and time itself. This explosion is not like that of a bomb because the bomb would throw matter away into the space, however at the big bang space did not exist so it was a self contained explosion where space itself exploded. In the subsequent sections we will analyse the most important pieces of evidence for the Big Bang theory.

The Expansion of the Universe

This is probably the strongest clue we have and it provides a firm foundation for the Big Bang theory. In 1929 Edwin Hubble published results that confirmed the expansion of the universe by measuring the spectrum of light from the galaxies around us. Hubble found that the spectrum was red shifted which meant that these galaxies were constantly moving away from the earth. The other important discovery that Hubble made was that the speed of recession was proportional to the relative distance of the galaxy from the earth, thus he formulated his law as stated in equation (1).

The Hubble law is just what the Big Bang theory predicts for a homogenous universe, and the fact that everything is rushing away from us is just a consequence of the big initial explosion that started the universe.

It may seem that if the universe is expanding and everything appears to be moving away from us, then we are in the centre of the universe. This is not quite true, and the balloon analogy is a good example to illustrate this. Imagine that we live on a surface of a balloon, as the balloon expands everything on its surface will appear to move away from us and this is the case whichever place we choose to be in i.e. there is no centre for the surface of a balloon. Taking into account the expansion of the universe, scientists showed

that if we allow time to go back the universe would have come together in a tiny super-heated state around 15 billion years ago.

The Cosmic Microwave Background (CMB)

The CMB was first predicted to exist by George Gamow in 1948 when he suggested that the early universe was very hot and dense. Two physicists Robert Dicke and P.J.E Peebles argued that we should still be able to observe the glow of the universe because the light from the very distant parts of the universe would just be reaching us now. However because the universe is expanding the radiation (or light) that will be observed will be greatly red shifted and it will appear as microwave radiation.

This was indeed observed by accident in 1965, by Arno Penzias and Robert Wilson at the Bell Telephone Laboratories in New Jersey. While they were testing a new microwave horn antenna designed to improve telephone calls Arno Penzias and Robert Wilson were very worried because their antenna was picking up an excess noise, this noise did not change no matter where they pointed the antenna. They happened to learn about the work of Dicke and Peebles and they soon realised that they had discovered the cosmic microwave radiation left over from the Big Bang.

The Big Bang theory not only predicts the existence of the CMB radiation but also its precise temperature. Figure 2 shows the predicted values of the CMB spectrum with the values obtained from the FIRAS experiment on NASA's COB satellite. There is an excellent agreement between both curves, even the error bars are too small to be seen. There is no alternative theory which predicts this precise spectrum except the Big Bang theory.

An important fact about the CMB is that it is very uniform and almost perfectly isotropic, only powerful telescopes such as WMAP (launched in 2001) can detect fluctuations in the CMB (WMAP resolves temperature differences, which vary by millionths of a degree (http://map.gsfc.nasa.gov/m_mm.html)). Figure 3 shows a recent map of CMB radiation obtained from WMAP mission. The fluctuations (which vary by a millionths degree) provide astronomers with valuable information about the Big Bang theory and the origin of galaxies and large-scale structures.

Nucleosynthesis of Light Elements

The Big Bang theory suggests that the universe was very hot and very dense, 1 second after the Big Bang the universe was 10 billion degrees in temperature; at such a high temperature all the matter of the universe was just a sea of isolated protons, electrons and neutrons. As the universe expanded and the temperature dropped, this allowed specific nuclear processes to occur. First a neutron combined with a proton to form Deuterium (heavy hydrogen), Deuterium in turn captured another neutron to form Tritium which interacted with a proton to form Helium. This process of light element formation in the early universe is known as the Big Bang Nucleosynthesis. Elements heavier than Helium, were created later in stars and spread widely by supernova explosions.

Theoretical calculations based on the Big Bang theory show that about a quarter (24%) of the ordinary matter in the universe is Helium, a result which is in accordance with the current stellar observations.

The Big Bang theory is the only model that accounts for the creation of stable Deuterium. In fact stars destroy this element, and besides this, the theory predicts a vast abundance of light element over heavy elements (with more light elements in earlier epochs), which is a confirmed observation. No other theory can justify the precise kinds of light elements we observe in superabundance except the Big Bang theory.

Formation of Galaxies and Large Scale Structures

The Big Bang model provides a good framework for the formation of galaxies and other large-scale structures. After the universe had cooled down to a specific temperature, the energy began to be dominated by massive particles rather than by any other forms (like radiation for example); this allowed the gravitational effects between massive particles to take effect, so that any small fluctuation in the density of matter would result in the collapse of matter to form galaxies and other large scale structure observed in the universe today. To account for the small density fluctuation, inflation theory was introduced. In this theory the universe went through a rapid (exponential) expansion shortly after the big bang. This rapid expansion is capable of producing small density fluctuations which were the seeds for galaxy and other large scale structures. Although inflation theory is still not proven, many cosmologists believe

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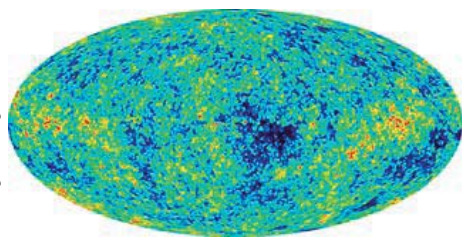


Figure 3: The Microwave Sky image from the WMAP mission

it is true as it provides answers to many difficulties the big bang theory has.

Hence the standard Big Bang model provides a framework in which we can understand galaxy formation, but inflation theory is still needed to introduce the fluctuations required responsible for the collapse of matter.

The Development and Fate of the Universe in the Light of the Big Bang

In the beginning just after the big bang, the four fundamental forces of nature: gravity, electromagnetic, weak nuclear and strong nuclear were all combined as a single force. At this first moment elementary particles like quarks, electron and neutrinos were created, and both the energy and density of the universe were very high.

During the Plank Time, after 10⁻⁴³ s, the universe is believed to have undergone a rate of expansion many times the speed of light (this does not violate relativity because space is expanding but no particles travel at the speed of light) this period is known as the inflationary epoch.

After 10⁻³² s from the big bang, the universe was just a sea of electrons, quarks and other subatomic particles, the extremely high temperature of the universe (10²⁷° C) prevented these subatomic particles from clumping together. As the universe expanded it cooled down and after 10⁻⁶ s, quarks were able to fuse, forming protons and neutrons.

Seconds after the big bang, when the universe cooled down to one million degrees, the formation of matter started to occur, protons and neutrons lost energy, which allowed nucleosynthesis to take place. The helium nucleus was formed as two protons and neutrons. For every helium nuclei formed, there were about ten protons left over which allowed 25% of the universe to be comprised of helium (Silk, 2001, page 141).

When the universe aged to 300,000 years, the temperature dropped to 10,000 K allowing helium nuclei to capture electrons and thus forming the first helium atom, at the same time hydrogen atoms were combining to form lithium.

After about 1 million years gravity made hydrogen and helium gas form giant clouds that became galaxies, and smaller clouds collapsed to form stars. As galaxies clustered together under the effect of gravity the first stars died and threw heavy element in the outer space, which allowed the formation of new stars and planets.

Even now after 15 billion years the universe is still expanding, but will this expansion continue for ever? Or will it come to end, in which case the universe will end up with a big crunch? It is the force of gravity that attracts galaxies to each other and thus acts to reduce the expansion rate of the universe and hence determine its fate. Thus we can easily conclude that the fate of the universe depends on the average density of matter in the universe.

If the average density of the universe is low, leading to a weak gravitational attraction between galaxies, the expansion of the universe would continue for ever in which case our universe is said to be unbounded or open. On the other hand, if the average density is high resulting in the gravity being strong enough to halt the expansion of the universe; then the universe will reach a maximum size before it starts collapsing as the gravity pulls galaxies back towards each other. In such a case we say that the universe is bounded or closed. Between the two cases there exists a special case in which the universe is marginally bounded. In this case the average density of matter is exactly equal to the critical density ρ_c leaving the universe close to collapsing. ρ_c is given in equation (2) in which H_0 is the Hubble constant and G is the universal constant of gravitation.

$$\rho_c = \frac{3H_0^2}{8\pi G} \quad (2)$$

The average density of matter in the universe is not known precisely and thus leaving the fate of the universe undetermined at least for the moment.

Beyond the Big Bang

Although the big bang theory provides a good framework to understand the evolution of the universe it does not resolve some fundamental issues: what happened just be-

fore the initial instant, the nature of the singularity itself, and the origin of galaxies?

In order to resolve these issues we need a completely new physics to look at what happened during the Plank Time or even before that. There are two obstacles that prevent us from doing this, the first one being that our current physics assumes a background of space and time, and the second one is the need for a quantum gravity theory or the theory of everything which is still not found yet.

The era of creation is where quantum physics and gravitation merge into a single theory because both are important (the scale is very small and the density is very large). There have been a lot of attempts to unify quantum physics with gravity and this has led to the formation of the Super String theory in which scientists try to unify the four fundamental forces of nature in one single theoretical framework. In the Super String theory we may need up to 11 dimensions to account for the unification of the fundamental forces and the energies dealt with are of the order of 10¹⁹ GeV, which makes it impossible to test this theory in a laboratory.

However in the early universe such energies existed and the big bang theory may play a central role in making us understand the era of creation near the singularity. This will not happen until the big bang theory is completed, because at the present time it lacks a beginning and we can not predict its ending.

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Pharmacokinetics in clinical trials of drug development

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In the drug development process, clinical trials are carried out to investigate the efficacy and safety of the new chemical entities. These investigations determine certain factors and parameters which help understand the behaviour of the drug inside the body. This behaviour could be either the way the drug affects the body in time, i.e. pharmacokinetics, or the way the body deals with the drug. Although clinical trials in drug development have evolved so much over the past few years as they now involve a series of biological and genetic investigations, pharmacokinetics still form a significant part of these clinical studies. Understanding how the pharmacokinetic parameters are determined or calculated during clinical trials is such a difficult and complicated task which will not be discussed here. However, an overview is given on the pharmacokinetic parameters involved in clinical trials in drug development.

Prior to making it into the market, medicines have to pass some vigorous clinical investigations to determine their safety and efficacy. Traditionally, these investigations were carried out by studying the pharmacokinetic properties of the new drugs. These properties cover the time course of the passage of the drug and its metabolites through the body (Griffin and O'Grady, 2002). Pharmacokinetics could also be thought of as the way the body affects the drug in time, while in contrast the way by which the drug affects the body is known as pharmacodynamics (Neal, 1997).

How a Drug Gets into Your Body?

Drugs are administered into the body either directly into the vascular compartment or by alternative routes. When a drug is delivered

intravenously, it is assumed that the entire administered dose reaches the systemic circulation. However, this is not the case for drugs delivered orally. This is due to the incomplete absorption or the metabolism of the drug in the mucosa of the gastrointestinal tract or the liver, i.e. first-pass metabolism (Griffin and O'Grady, 2002). Once in the systemic circulation, the drug is then distributed around the body so that it reaches its site of action. This is then followed by the drug's removal, either by being metabolised to other molecules or by removal from the plasma into the urine or bile in a process known as excretion. In pharmacokinetics, metabolism and excretion are collectively referred to as elimination.

The drug concentration in the body is usually taken as the plasma drug concentration, as it is impossible to measure the drug concentration at its site of action. Yet, drug concentrations could also be measured from other bodily fluids such as the saliva and from the excreta, i.e. urine and faeces. Although it is usually a complex relationship, there is in fact a direct relationship between the drug plasma concentration and the response. This relationship could be used to design the dosing regimen of the drug in healthy individuals, in the presence of organ failure and/or concomitant medications (Griffin and O'Grady, 2002).

Factors Affecting Drug's Plasma Concentration

The drug's plasma concentration is affected by many factors including its absorption, distribution, metabolism and excretion. Consequently, these factors affect the body's response to the drug. The effects of the pharmacokinetic factors on the drug's plasma concentration, following oral delivery, are summarized by the plasma concentration-time curve (Figure.1).

Following administration, absorption of the drug is the first pharmacokinetic process that takes place, which leads to an increase in the plasma drug concentration. As soon as there is some drug in the plasma, distribution and elimination will start. This is followed by slow drug absorption, as there would be less drug to be absorbed. An even stage will then be reached when the rate of the drug absorbed will equal the rate of drug eliminated from the systemic circulation. After that, absorption continues to slow while elimination increases resulting in a decreased drug plasma concentration. Elimination is usually slower than distribution, resulting in an initial fast fall, due mainly to distribution and then a slower fall due to elimination (Thomas, 2000). The factors affecting the drug plasma concentration are summarized below.

Received: March 16, 2006; Revised: March 21, 2006;
Accepted: April 4, 2006; Published April 16, 2006.

The author declares no conflict of interest.

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Academic Editor: Younes MOKRAB, Department of Biochemistry, University of Cambridge, UK. younes@cryst.bioc.cam.ac.uk.

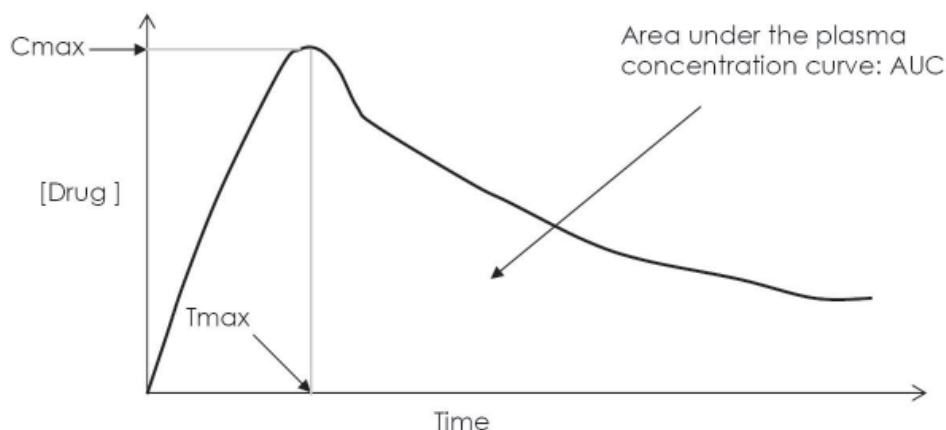


Figure 1: Plasma concentration-time curve following oral delivery

Absorption

This is the passage of a drug from its site of administration into the plasma (Rang, Dale and Ritter, 1999). This concept is very important for all routes of administration except the intravenous route in which the absorption is assumed to be 100%. Absorption is achieved at numerous sites in the body depending on the route of drug delivery. When drugs are delivered orally, their major site of absorption is the small intestine whereas for sublingual administration the drug absorption is achieved via the oral cavity (Rang, Dale and Ritter, 1999). In addition, for inhaled drugs, absorption is achieved in the lungs. Drug absorption is affected by numerous factors including the drug's physicochemical properties, e.g. pKa, molecular weight and lipid solubility, and the conditions at the site of action, e.g. the gastrointestinal motility and pH (for oral delivery) (Aulton, 2002). Once the drug reaches the systemic circulation, the drug distribution takes place.

Distribution

This process involves the transfer of the drug from one site in the body to another, and back again (Griffin and O'Grady, 2002). It could also be seen as the distribution between the systemic circulation and other tissues and fluids, which is usually a rapid and reversible process (Rang, Dale and Ritter, 1999). Drug distribution can be affected by numerous factors such as the local blood flow and the body physiological barriers (e.g. Blood-brain barrier). Such barriers can limit the drug distribution to certain parts of the body e.g. the brain. For example, the molecular weight and other physicochemical properties have great influence on the

drug's ability to cross the blood-brain barrier (Aulton, 2002).

Metabolism

During drug metabolism, which is also referred to as biotransformation, drugs are converted to other products before and after they have reached their sites of action (Thomas, 2000). Most of the reactions involved are catalyzed by enzymes and are known as Phase I and Phase II reactions. The metabolites produced from Phase I and II reactions are easily excreted as they are more water soluble than the parent drug. In Phase I reactions, this is achieved by the introduction of polar water solubilising groups or unmasking polar water soluble-solubilising (Thomas, 2000). In phase II, the water solubility is a result of combining a water-solubilising reactant with the drug to form a highly polar derivative.

Drug metabolism is affected by a number of factors including age. The ability to metabolise drugs is lower in the very young, under 5 years, and the elderly, over 60 years (Thomas, 2000). Gender also affects metabolism. Although the metabolic pathways followed by drugs is expected to be the same for males and females, differences are seen for drugs such as anxiolytics and hypnotics (Thomas, 2000). Genetic variation is another factor that influences drug metabolism. Due to genetic variations, some individuals may lack or have low concentrations of certain enzymes that are responsible for the drug metabolism, and this results in different pharmacological responses for the same drug (Griffin and O'Grady, 2002; Thomas, 2000).

Excretion

Excretion is usually thought of as the loss of chemically unchanged drugs (Rang, Dale and Ritter, 1999). However, it could also involve the excretion of the drug metabolites, which result from the metabolism of the parent drug. Excretion is achieved via three routes; the kidneys, the hepatobiliary system and the lungs (Rang, Dale and Ritter, 1999). Although it is rare, drugs can also be excreted in secretions such as milk and sweat. Excretion via these routes is quantitatively negligible compared with renal excretion. Thus, renal function can hugely affect the drug excretion and should be monitored especially prior to taking drugs, which result in (toxic) metabolites that are excreted via the renal system.

Quantifying the Drug Response

Practically, the factors discussed above are measured by studying the factors of the drug's clearance (CL), bioavailability (F) and volume of distribution (V_d).

Clearance

Clearance, CL , is the volume of blood in a defined region of the body that is cleared of a drug in a unit time (Thomas, 2000). It could also be defined the volume of plasma completely cleared of the drug per unit of time, and it can be calculated by dividing the rate of drug elimination by the plasma concentration (Griffin and O'Grady, 2002). Quantitatively, clearance has the units of flow (ml/min or l/hr) but it is usually corrected for body weight and given the units ml/min/kg. Clearance is mainly carried out by the liver and kidneys, yet other organs such as the lung and the gut, can take part as well. Generally, unless it is specified, clearance usually refers to the "total plasma clearance", which is expressed as the sum of all organ clearances ($CL_{total} = CL_{renal} + CL_{hepatic} + CL \dots$) (Griffin and O'Grady, 2002).

Bioavailability

Bioavailability, F , refers to the proportion of the administered drug dose that reaches the systemic circulation (Griffin and O'Grady, 2002). It is also defined as the fraction of the dose of a drug that enters the circulatory system (Thomas, 2000). Bioavailability values are unitless and they are usually expressed as percentage with values ranging from 0 to 100%. Following intravenous (IV) delivery

the bioavailability is taken as 100%, whereas for oral delivery the values are lower because of the incomplete absorption or the metabolism of the drug by the gut wall or liver, i.e. first-pass metabolism. Bioavailability can be calculated by dividing the area under curve of plasma concentration curve following oral delivery (AUC_{oral}) by the AUC_{iv} (Griffin and O'Grady, 2002).

Volume of distribution

Volume of distribution, V_d , is defined as the proportionality constant relating the amount of the drug in the body to the plasma concentration (Griffin & O'Grady, 2002). Thomas (2000) defines volume of distribution as a measure of the total volume of the body perfused by the drug. It is usually given the unit litre (l), which is corrected for body weight (l/kg) (Griffin and O'Grady, 2002; Thomas, 2000). The volume V_d could be calculated by dividing the total amount of the drug that is in the system by the drug plasma concentration.

Half-life

Another important Pharmacokinetic parameter is the drug's half-life, $t_{1/2}$. This is the time

taken for the concentration (of a drug in solution) to reduce by half (Aulton, 2002). Thomas (2000) defines the half-life as the time taken for the concentration of the drug to fall half its original value. It is determined by both volume of distribution (V_d) and clearance (CL) (Griffin and O'Grady, 2002), as given in the equation below;

$$t_{1/2} = 0.7 V_d / CL$$

Half-life values are used in determining dosing regimens, as the frequency of dosing is adjusted to keep the fluctuation of concentration between doses within acceptable limits (Griffin and O'Grady, 2002). The plasma elimination half-life varies from one drug to another. For some drugs it can be too short (few seconds or minutes) or too long (weeks). Hence, in order to produce pharmacological response, drugs with short elimination half-life are dosed more often than those with long half-life.

Conclusion

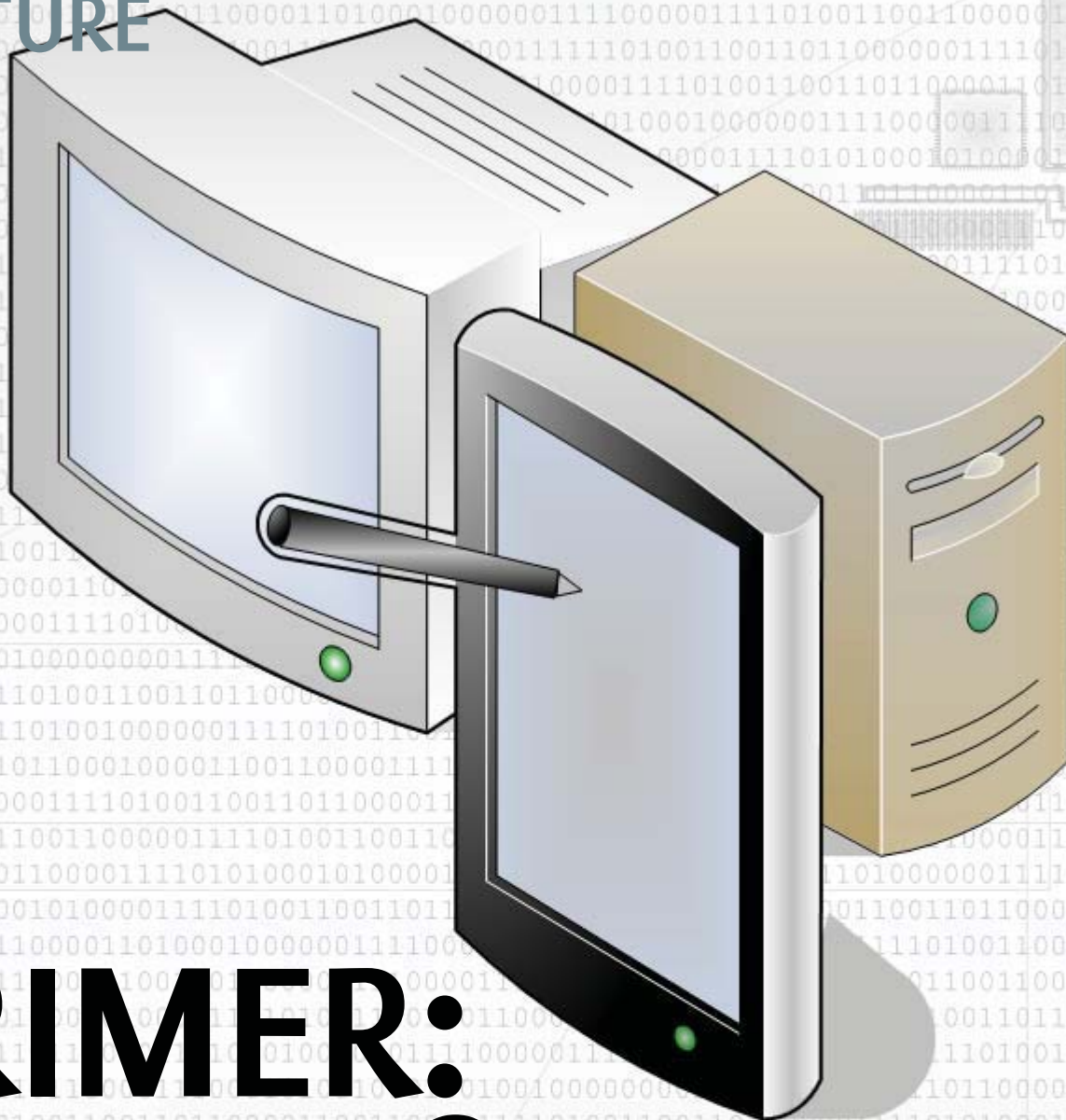
Pharmacokinetic investigations have served, for a long time, as the main source of information of drugs undergoing clinical trials studies. However, these investigations failed to provide certain essential information such

as the prediction of the variability of the drug response. Although these failures have not resulted in the pharmacokinetics studies being excluded from clinical trials, they have indeed led to the introduction of pharmacogenetics. Thus, nowadays, both pharmacokinetics and pharmacogenetics form an integral part of the clinical trials of drug development.

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FEATURE



PRIMER: COMPILER OPTIMISATION

Improving Locality via Loop and Data Transformations

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One of the main important areas in computer science is Computer Programming. Computer Programming, often referred to as simply “programming”, is the art of implementing one or more inter-related abstract algorithms using a particular programming language. The result, a program, is then compiled in order to produce an executable computer program. The compilation stage is performed by a compiler, another computer program, which transforms the program source code into an executable application. Compilers often include optimizers which optimise the program being compiled for some measure, e.g. time or space.

In this article, we give a brief introduction into the craft of computer programming and compilation. We then introduce the notion of program optimisation and compare the traditional optimisation techniques, known as source code transformations, and the more recent data transformations.

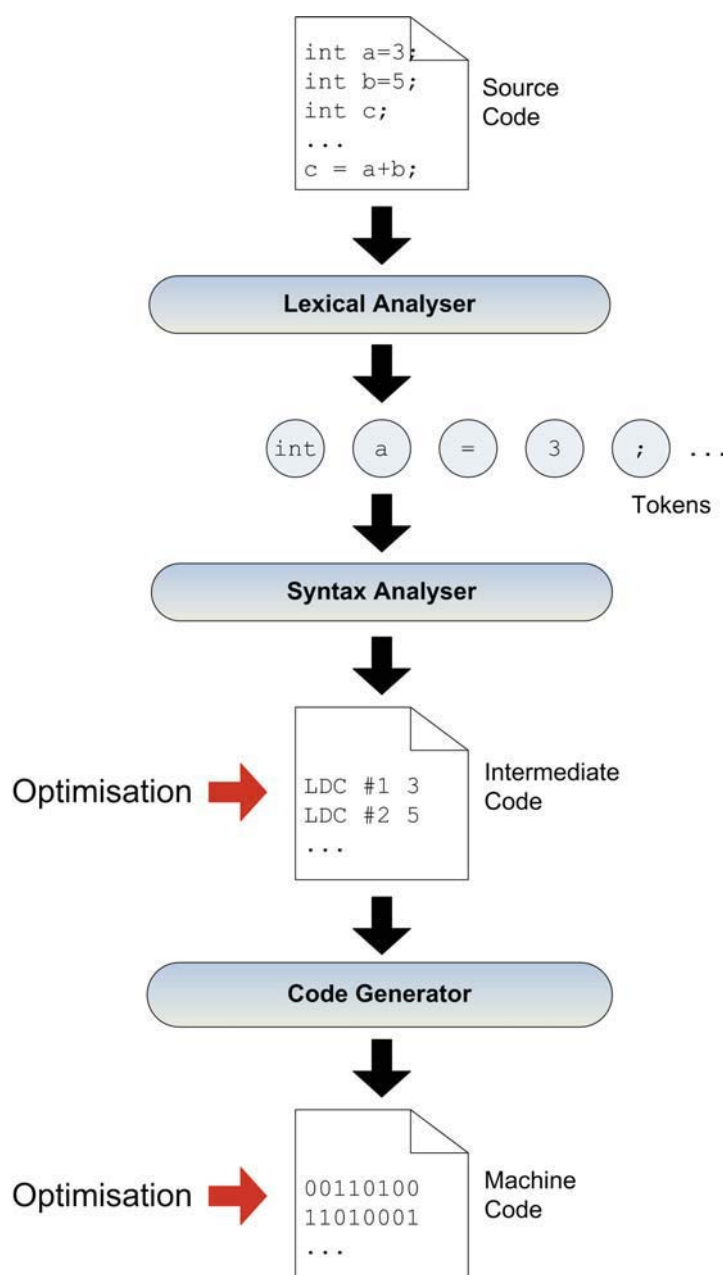


Figure 1: The stages of a typical compiler

Computer Programming: An Overview

Computer programming is a blend of art, science, mathematics and engineering. This is used to produce a robust, efficient and correct program that performs the required functionality in minimal time and space. On its own, a computer program is a simple text file containing from one to thousands of lines of program code. The program code, also denoted as source code, is written by the programmer,

following the semantics and grammar of particular programming language.

There exist many programming languages. Formally, a programming language is a standardised communication technique for expressing instructions to a computer, which enables a programmer to precisely specify what data a computer will act upon, how data will be stored/transmitted, and what actions will be taken under various circumstances.

The analogy used for computer languages is similar to one used for natural languages. Each programming language is defined using a grammar, which is composed of a set of alphabet and a set of rules. The alphabet of a programming language is the set of key words that the language recognises; and is governed by a set of rules which describe precisely how a program can be written using the language. Thus, each language has its own (distinct) grammar.

Despite the formal similarities, computer languages differ considerably. They support different constructs and require different levels of detail to be handled by the programmer. The C language, for example, provides the programmer with powerful memory manipulation tools known as pointers.

Data Access and Organisation

A computer program can hence be considered as a composition of data and actions. Every program stores some sort of data, in varying forms and sizes, and defines which actions are to be taken on that data. The data typically represent information in the real world such as names, bank accounts and measurements and are characterised by unique names in the program. However, inside the computer, all data is stored in binary format, i.e. using a sequence of zeros and ones and the only way the data in the computer can be read or modified is through the program and the compiler. Depending on many factors, such as the size of the data, the algorithm used and the programming language, the data in a computer program can be organised into data structures. In computer science, a data structure is a way of storing data in the computer to facilitate its access and make the program more efficient, saving execution time and/or memory space.

Compilation

Although the choice of languages presented to the programmer is diverse, the computer does not have much choice. The only programming language that a computer can di-

Received: March 04, 2006; Revised: March 25, 2006; Accepted: March 30, 2006; Published: April 16, 2006.

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rectly execute is machine language. Originally, most programmers wrote their programmes in machine language, but this is very rare nowadays despite the great flexibility and level of details it provides. The main reason for this is that the task of writing programs in machine language is very time consuming and more error-prone. In addition to this, debugging programmes written in this language is very difficult which makes maintaining them very hard.

This complexity has given rise to the art of compilation. Using a compiler, all the programmers are required to do is write the source code in some language and let the compiler translate it into machine code. The translation process passes through several steps to ensure the correctness of the input program and produce an optimised equivalent in machine code. The stages of a typical compiler are shown in Figure 1.

The term “compiler” has been known since the 14th century. In its literal sense, a compiler is a person who compiles data, meaning producing a list, book or report by assembling information from other sources (The New Oxford Dictionary). By analogy, the term “compiler” in Computer Science denotes a tool that produces a program, using information acquired from other sources. These sources being the same program written in a different language, a compiler is then defined as a software tool that translates a computer program from one form to another.

For a more formal definition of a compiler, we refer to Aho et al. (Aho et al., 1986):

A compiler is a program that reads a program written in one language, the source language, and translates it into an equivalent program in another language, the target language.

Most compilers translate a source code text file, written in a high level language to object code or machine language that may run on a computer or a virtual machine. This translation usually involves many steps at which the program is translated into other forms called intermediate languages or representations. Compilers, in computing terms, have existed for a little more than half a century.

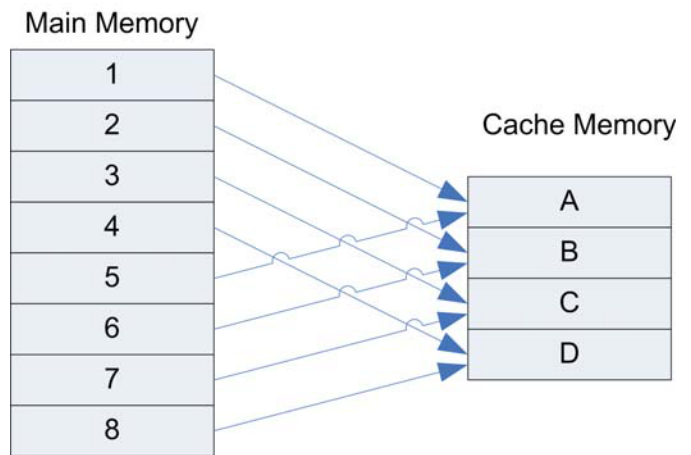


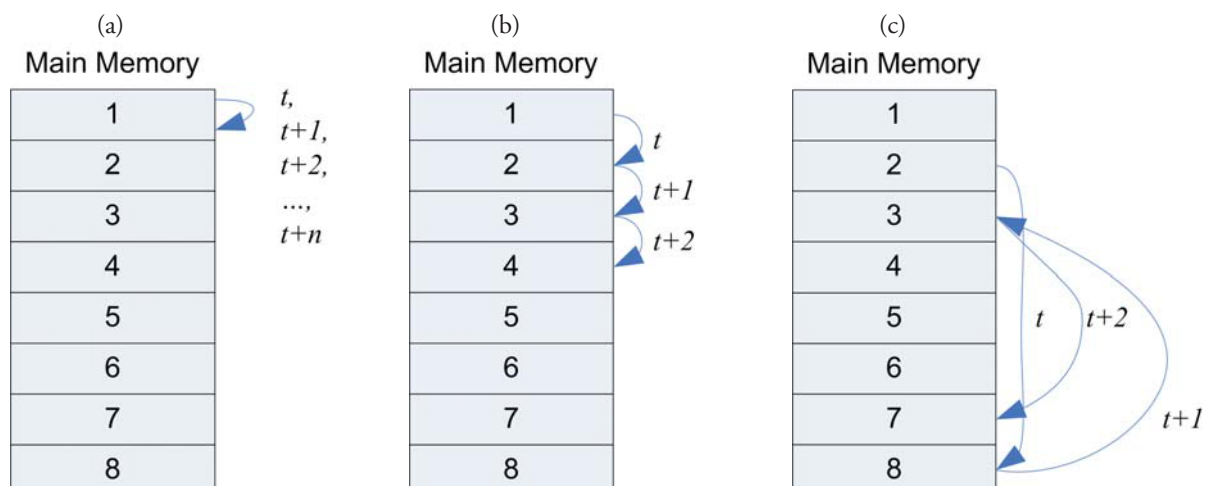
Figure 2: An example mapping from main memory to cache memory

In the 1950s, several experimental compilers were developed. Grace Hopper (1906-1992), also known as the Mother of Cobol, developed the A-0 System by 1952. The system, which was a set of instructions that could translate symbolic mathematical code into machine language, was later improved by versions A-1 and A-2. The A-2 compiler was the first compiler to be used extensively, paving the way to the development of programming languages.

However, the first complete compiler was introduced in 1957 by the FORTRAN team led by John Backus at IBM. After this, the idea of compilation quickly caught on, and most of the principles of compiler design were developed during the 1960s.

Early compilers used to be implemented in assembly languages and the use of high-level languages for writing compilers did not gain popularity until the early 1970s, when Pascal and C compilers were written in the Pascal and C respectively.

Figure 3: Examples of data access. (a) Accesses exhibiting temporal locality. (b) Accesses exhibiting spatial locality. (c) Accesses exhibiting poor locality.



Optimisation

The complexity of programming and compiling a program is often proportional to the complexity of the underlying functionality. Computer programs are very diverse and range from simple text printing program to a complex 3-dimensional game. By definition, program optimisation is modifying a computer program to improve its efficiency with regards to some measure such as memory usage, execution speed, power consumption, etc.

There are several resources for which the program can be optimised, which creates many trade-offs. For instance, making a program run faster may increase the size of its code, and hence require more memory usage. Consequently, optimisation usually focuses on one or two measures.

Generally, optimising a program requires finding its bottleneck. The bottleneck of a program is the critical part of the code in which most of the overall resource is consumed. On average, 80% of the execution time of a program is spent on performing operations that are described in only 20% of the code. The most popular bottlenecks in today's applications are loops, which are programming constructs used specifically to achieve consecutive accesses to multiple memory locations. A loop can be single, having depth 1; or nested, having depth larger than 2. A nested loop of level l is composed of l different loops executed in a hierarchical way where the loop at level 1 is called the outermost loop and contains $l-1$ loops and an arbitrary loop at level k contains $l-k$ loops.

Cache Memory

A cache is a small memory providing fast access to data in a computer. It stores a collection of data duplicating the original values stored elsewhere, such as on the main memory, on a disk or on a web server, where it is usually more expensive, in terms of access time, to fetch data elements. Once the data is stored in the cache, future use can be made by accessing the cached copy rather than re-fetching the data from its original source, so that the average data access time is lower.

Cache memory operates in blocks. When a data element is accessed in main memory, the whole block to which the element belongs is moved to the cache. A diagram showing a simple mapping from main memory to cache memory is shown in Figure 2. Subsequent accesses to the same element or elements in the same block are then performed on the cache, until the block is replaced. A block of data is thrown out of the cache if another block from memory is mapped to the same cache location. Note that since the size of the cache is much smaller than the size of main memory, there might be several data blocks which are mapped to the same cache location.

When a block of data is removed from the cache, the new values are rewritten in the main memory, to preserve data correctness.

Locality of Access

In the context of programming, caches can be very useful. Usually, computer programs access the data they use in a pattern that exhibits high locality of reference. Locality of reference denotes the process of accessing a data source multiple times. Here we distinguish two different kinds of locality:

Temporal Locality: This term is used to denote multiple accesses to the same data element. This is also known as proximity in time.

Spatial Locality: This term is used to denote consecutive accesses, which occur in short time intervals, to elements that are stored near each other on memory. This is also known as proximity in space.

These two notions are illustrated in Figure 3. In (a), the same location, 1, is accessed in short times intervals. In (b), the program accesses locations 1, 2, 3 and 4 in times 0, t , $t+1$, and $t+2$. In (c), on the other hand, locations 2, 8, 3 and 7 are accessed in consecutive times, which results in poor locality.

Memory Space as a Bottleneck

The processing power of high performance computers continues to increase dramatically. In the same time, the rate of increase of the speed of memory subsystems has not kept pace with the rate of improvement in processor speeds (Hennessy, 1999). Therefore, modern multiprocessors include several levels of memory hierarchy in which the lower levels are slow and inexpensive (e.g. disks, memory) while the higher levels (e.g. caches) are fast but expensive.

On most modern machines, accessing a nearby memory location is much cheaper than accessing a farther location. Previous studies have shown that large scientific programs spend as much as a quarter to a half of their execution times waiting for data from memory (Torrie et al., 1995). In order to eliminate this memory bottleneck, data accesses in the program need to be carefully organised to take full advantage of locality of reference. Specifically, the aim is to ensure that the data needed by the program is available in the cache at the time when needed.

Loop Transformation

Memory access bottlenecks are often associated with loops. The classical way of exploiting cache locality is to transform a loop accordingly. Previous research in this direction has greatly focused on loop transformation and several loop transformations have been implemented to improve data locality (Frabouet et al., 2001; Marchal et al., 2004; McKinley et al., 2004). Many recent works have provided more advances in loop transformation theory. By using affine representation of loops, several loop transformations have been unified into a single framework using a matrix representation of these transformations (Kandemir, Choudhary, Ramanujam et al., 1998; Wolfe and Lam, 1991;

Wolfe, 1996). The details of this framework are beyond the scope of this article.

The main aim of loop transformations is to alter the structure of the loop so that the order of computations inside the loop is re-ordered. Re-ordering the computations naturally leads to a new pattern of access to the data used in them. The new pattern, which must preserve computation dependencies, will exhibit better data locality and improve the execution time of the loop. For example, optimising the locality of access shown in Figure 3 (c) using loop transformations results in the new access pattern depicted in Figure 4 (a).

As the figure shows, the order in which the data is processed has been changed in a way that locations 2, 3, 7 and 8 are accessed in short time intervals.

However, loop transformations have some drawbacks which are summarised below:

1. Loop transformations may not always be legal due to dependence constraints (Wolfe, 1996). Data dependencies in a loop nest may not allow a loop transformation to improve locality.
2. It might be difficult to find a loop transformation that improves the locality of all the arrays referenced in the nest.
3. Loop transformations affect all accesses to data, usually stored as arrays, in the body of loop. This is dangerous as some references may be adversely affected.
4. Loop transformations are not very successful in optimizing locality for complex loops structures. Kodukula and Pingali (Kodukula et al., 1996) show that handling such loops within a loop transformation framework requires a different approach to the problem.

Data Transformation

The layout of data in memory represents the most significant impact on the performance of scientific computations on multiprocessor machines. As shown earlier (O'Boyle and Knijnenburg, 1997; Leung and Zahoran, 1995; Kandemir, Choudhary, Shenoy et al., 1998), techniques that decide good data layouts can improve the performance of programs which access a large amount of data stored in arrays, such as image processing applications.

To overcome the limitations of loop transformations, some techniques have been recently proposed to optimize spatial locality in a loop nest using data space (array layout) transformations (O'Boyle and Knijnenburg, 1997; Leung and Zahoran, 1995). Such a transformation typically modifies the memory layout of arrays.

Data transformations work by changing the order of storage of data elements in memory, as opposed to changing the order of access. The new layout of data is decided by considering the order in which elements are accessed. This order is then modelled in memory. This is illustrated in Figure 4 (b). In this example, the order of computation is

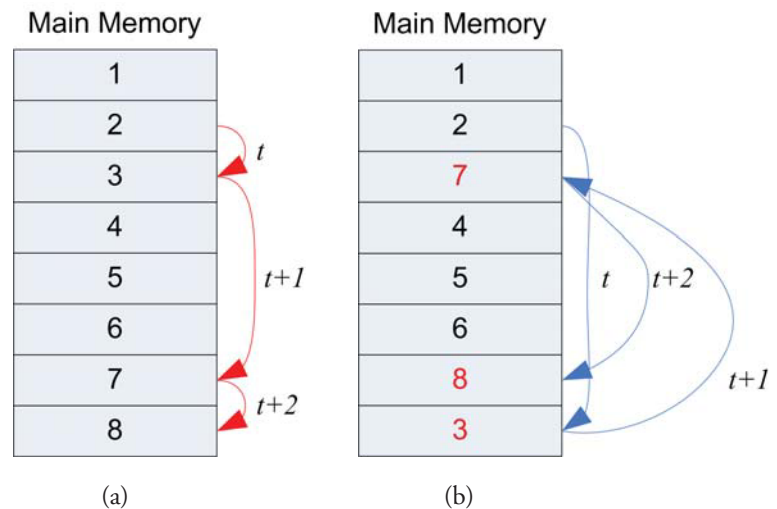


Figure 4: Locality optimisation. (a) via loop transformation. (b) via data transformation

unchanged; however, note that the contents of locations 3, 8 and 7 have been replaced in order to improve locality of reference.

The use of data transformations is a solution to the limitations seen in loop transformations. This is detailed below:

1. First of all, they are not constrained by data dependencies. This makes them more widely applicable than traditional loop transformations. In some programs, even if loop transformations are legal, data transformations may result in better improvement.
2. Data transformations modify one array at a time and therefore affect the consented array only. Accesses to other arrays, whether inside or outside the same loop, are not affected.
3. Data transformations are easily applicable to complex loops as they do not change the computation order.
4. Data transformations sound to be very powerful and efficient. However, the main problem with them is that it is hard to identify the optimal layout of data in memory. Their impact is global and their effect goes beyond a single loop boundary.

For example, transforming the memory layout of a multi-dimensional array from column-major to row-major to improve the locality of a reference to the said array in one loop nest can adversely affect the locality of the other references to the same array in other loop nests. When a given data layout is determined by optimizing one reference in a loop, this layout is propagated to all the other references to the same array in the program. Other loop transformations may be needed to take advantage of this layout. Here, one more complication may arise if such transformations may not be valid due to data dependencies or may be incompatible with other references.

Conclusion

In this article, we have given a general overview of loop and

data transformations. There is no doubt that data locality is an important goal to achieve in order to optimise the execution of the program. Although data transformations are much nearer to this goal than loop transformations, there are still some cases which they cannot handle. This suggests that a unified framework that employ both and data transformations is much need to achieve optimal results.

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Interview with Dr Laiche Djouhry

Prologue: Inflammation Firing Pain

Pain sensation had for a long time puzzled philosophers, before it fascinated scientists to embark with empirical scientific research. In his book, "L'Homme", Descartes portrayed the pain pathway as "delicate threads", which connect the body to the mind. Although this idea was rather inspiring at the time, such a simplistic intuition hampered the understanding of pain. It is now known that pain is far more than just 'pure sensation' rather it is a convoluted phenomenon with intimate interplay between sensory and cognitive mechanisms. It is simply challenging to encapsulate all aspects of pain in a single definition, which range from simple sensation to complex emotional experiences. In the hope to decipher the interlinked aspects of pain, pain research has become an important discipline in physiology, neuroscience and even psychology. Here, Dr Laiche Djouhri, an Algerian senior scientist working at the University of Bristol shares some of his thoughts about pain research in general and most importantly his recent finding published in The Journal of Neuroscience in relation to spontaneous pain.

Dr Djouhri will expand on this subject in an invited review in the next issue of IBS Journal of Science.

Press Release (The University of Bristol January 24, 2006)

New research shows that it is undamaged nerve fibres that cause ongoing spontaneous pain, not those that are injured.

These unexpected findings, by Dr Laiche Djouhri, Professor Sally Lawson and colleagues from the University of Bristol, UK, are reported in the Journal of Neuroscience [25 January, 2006].

Previous research into ongoing chronic pain has tended to focus on the damaged nerve fibres after injury or disease and overlooked the intact fibres. This new understanding may help pharmaceutical companies formulate novel pain killers.

Professor Lawson said: "The cause of this ongoing pain and why it arises spontaneously was not understood before. Now that we know the type of nerve fibres involved, and especially that it is the undamaged fibres that cause this pain, we can examine them to find out what causes them to continually send impulses to the brain. This should help in the search for new analgesics that are effective for controlling ongoing pain."

"Chronic pain is a devastating and widespread problem, affecting one in five adults across Europe." Professor Sally Lawson. Ongoing pain is a burning or sharp stabbing/shooting pain that can occur spontaneously after nerve injury. Unlike 'evoked' pain caused, for example, by hitting your thumb with a hammer, ongoing pain is particularly difficult to live with because it is often impossible to treat with currently available pain killers.

Djouhri and Lawson show that the nerve cells responsible are 'nociceptors' or damage detectors. There are thousands of these nerves cells, each of which has a very long, fine nerve fibre emerging from it. These fibres run within nerves and connect the skin or other tissues to the spinal cord.

When activated through damage or disease, these nerve fibres fire electrical impulses that travel along the fibre from the site of injury to the spinal cord, from where information is sent to the brain. The faster the undamaged fine fibres fire, the stronger the ongoing pain becomes.

Dr Djouhri added: "The cause of this firing appears to be inflammation within the nerves or tissues, caused by dying or degeneration of the injured nerve fibres within the same nerve."

The mechanism described by Djouhri and Lawson occurs following nerve injury and in nerve and tissue inflammation. Further research is now needed to establish how generally this mechanism may contribute to ongoing pain associated with a wide variety of diseases such as back pain or shingles.

IBS_{Scientific}: Before we start, IBS_{Scientific} team congratulates you for your recent work published in the Journal of Neuroscience.

1. IBS_{Scientific}: How did you get into the field of pain research?

Well, I have always been fascinated by the nervous system and how it processes sensory information. In fact my final year project as an undergraduate (animal biology) involved work on the nervous system at the University of Constantine. So to learn more about the system I did my PhD in Neurophysiology at Sheffield University and my PhD project was directed towards how transmission of sensory information particularly pain information is modulated by CNS depressants (e.g. anaesthetics) at the level of the thalamus. Then I worked for about 5 years as a Postdoc at Edinburgh University where I was investigating how sensory information is processed at the level of the spinal cord. More recently and since moving to Bristol University, I have become even more interested in pain research and been interested in the role of primary sensory neurons in chronic pain i.e., the neuronal mechanisms underlying hypersensitivity associated with chronic pain states. So as you can see I started my research career by looking at transmission of pain information in the CNS and more recently been interested in the role of peripheral nervous system in chronic pain.

2. IBS_{Scientific}: Could you tell us a little bit about the model system you use for studying chronic pain?

Before I tell you about the animal model that we use to study chronic pain, I think it would be helpful to firstly define what is meant by chronic pain. Pain is described as chronic when it lasts for 3-6 months or longer or the pain that persists beyond the time expected for an injury to heal or an illness to end. But it can last for years or even lifetime and becomes an illness itself rather than a symptom of a disease. Chronic pain is abnormal and 'bad' because it serves no useful function and its cause is often not easily identified (multifactorial). Chronic pain affects 1 in 5 of adult Europeans and costs the European economy about 25 billion pounds per year according to a recent survey that involved 46,000 people across Europe. Chronic pain can be either inflammatory associated with tissue injury/inflammation or neuropathic associated with nerve injury/dysfunction. It is characterized in humans by spontaneous pain, allodynia (pain in response to a normally non-painful stimulus, e.g., touch as when you have tissue inflammation) and hyperalgesia (exaggerated pain to a normally painful stimulus).

In contrast, acute pain is a physiological (normal) pain and is 'good' because it plays a protective role and acts as a warning system or device to warn us of immediate threats and this why it is sometimes referred to a warning pain. Unlike chronic pain, the cause of acute pain is known and the pain resolves spontaneously; it can be somatic originating from bones, joints, muscles or visceral originating from internal organs, e.g. stomach.

Let me now tell you about the animal model that we use to study chronic pain. We have animal models for both chronic inflammatory and neuropathic pain. For chronic neuropathic pain (our topic), we use a modified version of a well established and widely used model known as spinal nerve ligation (SNL) model or 'Chung' model (De-

Implications of the discovery... What do the experts think?

The effect of the discovery on our understanding of spontaneous pain:

'Jeffrey Mogil, the EP Taylor professor of pain studies at McGill University in Montreal, Canada, found the research stunning. "The important thing here is that all of drug development for pain in the past 50 years has been looking at how drugs work, and no one has looked at spontaneous pain. The reason for the problem may have been people were studying the wrong symptom," he said.

"This will help force a shift on how pain research is done -- a shift for the better," professor Mogil added.

WASHINGTON, Jan. 25 (UPI) —'English researchers have pinpointed the exact cause of chronic pain, possibly opening the door for revolutionary new treatments'.

veloped by Kim and Chung in 1992), which involves tight ligation with a suture of lumbar (L5) spinal nerve. Our modified SNL model (mSNL) involves in addition to ligation and transection of L5 spinal nerve, loose ligation of the adjacent L4 spinal nerve with chromic gut to induce inflammation of the L4 spinal nerve (Figure. 1). In other words our model involves injury (cut) of one spinal nerve (L5) and inflammation of uninjured (L4) spinal nerve. Unlike the original SNL model, our mSNL model showed significant spontaneous foot lifting which is a behavioural sign of spontaneous (ongoing) pain, an important aspect of neuropathic pain in humans.

3. IBS_{Scientific}: In your latest paper, published in The Journal of Neuroscience, you reported some significant findings regarding the physiology of spontaneous pain. Could you talk us through the main findings of the paper?

Before summarizing our main findings, I would like to firstly define spontaneous pain and why we are interested in it. Spontaneous (ongoing) neuropathic pain is a burning or sharp stabbing/shooting pain that can occur spontaneously after nerve injury. Unlike the evoked aspect of neuropathic pain (allodynia and hyperalgesia) caused, for example, by moving the affected part, spontaneous pain is particularly difficult to live with because it is unavoidable and often impossible to treat with currently available pain killers.

The main findings of our study are that:

a) Spontaneous pain behaviour is unexpectedly, linked to the rate of spontaneous firing (stimulus independent) in uninjured (intact) fine nerve fibres NOT injured nerve fibres. In other words, the faster the undamaged fine fibres fire, the stronger the ongoing pain becomes. These fine (thin) nerve fibres known as nociceptors "damage detectors" fire electrical impulses (action potentials) that travel along the

Figure 1. A schematic diagram of the experimental set up. The modified spinal nerve ligation (mSNL) model involved transection of L5 spinal nerve (nerve injury) as well as loose ligation of the L4 spinal nerve (nerve inflammation). Note that sharp glass microelectrodes were used to record, in anaesthetized rats, action potentials (nerve impulses) intracellularly from dorsal root ganglion (DRG) neurons. And that stimulating electrodes are used for electrical stimulation of the cut dorsal root. The peripheral endings of these neurons are specialized in detecting and translating various forms of stimulus energy into a neuronal signal or action potential which is then conducted along the axon into the CNS. The "pain" signal originates in these neurons.

nerve fibre to the spinal cord, from where 'pain' information is sent to the brain to be perceived.

b) The cause of this firing in uninjured nerve fibres appears to be inflammation within the nerves or tissues, caused by dying or degeneration of the injured nerve fibres within the same nerve.

4. IBS_{scientific}: What is the current model for the physiology of spontaneous pain? What does your current study add to the current model?

To my knowledge, our model is the only model that shows significant and consistent signs of spontaneous pain. This is because as Professor Mogil confirms (see box) the spontaneous aspect of neuropathic pain has been, until now, overlooked and most previous research into chronic neuropathic pain has tended to focus on the role, in evoked pain, of damaged nerve fibres after injury or disease and overlooked the intact fibres.

5. IBS_{scientific}: How long did this work take?

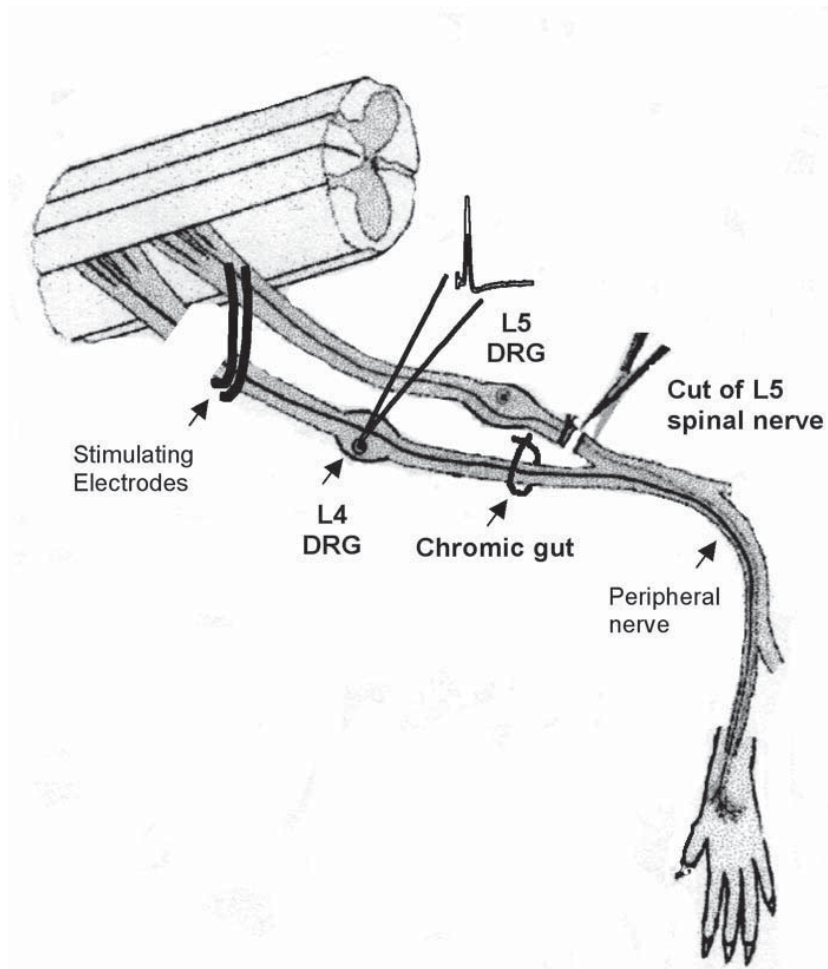
It took about 2 years from starting the experiments to publication of the paper.

6. IBS_{scientific}: What are the implications of your discovery on translational and clinical research?

Our findings are exciting and should encourage investigators in the field to focus on uninjured nerve fibres and examine them to find out what causes them to continually send impulses to the brain (see box). So further work is needed to determine how the increased firing in the uninjured fine fibers could be prevented (by novel analgesics) in order to alleviate the ongoing pain.

7. IBS_{scientific}: Finally we wish you all the best with your current and future work and thank you for your time

Thank you for giving me an opportunity to tell you about my recent research work and to share with you some of my thoughts.



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